^{99}Tc-MDP in Postmenopausal Women With Differentiated Thyroid Cancer and Osteoporosis

Trial registration: NCT02304757

April 16，2021

Study Protocol

Study Type: Interventional

Study Design: Treatment, Parallel Assignment, Single Blind (Outcomes Assessor), Non-Randomized, Efficacy Study

Patients recruitment

This was an open-label, prospective non-randomized study carried out in three centers (ClinicalTrials.gov ID: NCT02304757) from November 2015 to December 2019. Postmenopausal women are eligible in the study fulfilling all the following criteria. (1) They were pathologically diagnosed with DTC including papillary or follicular carcinoma. (2) They received a near total thyroidectomy and radioiodine treatment. (3) TSH suppression should be at least one year before the study. (4) Bone mineral density (BMD) in lumbar spine and/or hip was tested by Dual-energy X-ray absorptiometry (DXA) at baseline, 6 month (m) and/or 12m follow up. 5) The diagnosis of osteoporosis was T-score $\leq$-2.5 SD at the lumbar spine, or hip.

We excluded patients considering the following criteria: (1) patients having medications for OS before TSH suppression treatment; (2) secondary OS; (3) severe liver or kidney disease; (4) myelosuppression; (5) digestive disease; (6) long term use of immunosuppressive agent, estrogen or estrogen receptor modulators. This study was approved by the Institutional Review Board of Hospital Research Ethics. All the patients were fully acquainted with their treatment and consented to participate in the clinical trial.

TSH suppression treatment

TSH suppression treatment was based on the risk stratification of DTC using levothyroxine (L-T_4) as recommended

Treatment protocol for osteopenia and osteoporosis

Patients with OS were divided into ^{99}Tc-MDP and alendronate treatment groups.

1. ^{99}Tc-MDP treatment group: 15mg ^{99}Tc-MDP were intravenously administered twice a week for 10 weeks, then once a week for 8 weeks, every two weeks for 22

weeks and monthly for another 3m.

2. Alendronate treatment group: 70mg alendronate (Merck & Co., Darmstadt, Germany) was administered orally once a week for 12m.

Laboratory assays

Bone alkaline phosphatase (ALP), osteocalcin and propeptide of type I procollagen (PINP), and C-terminal telopeptide of type I collagen (CTX) were all determined by enzyme-linked immunosorbent assay (Modular E170, Hoffmann-La Roche, Basel, Switzerland). Free T_3, free T_4, thyroid stimulating hormone (TSH) was measured using a time-resolved immunofluorometric assay (Anytest, sym-bio lifescience co., ltd, Shanghai, China). 25(OH) D, parathyroid hormone (PTH), serum calcium and phosphorus and other laboratory tests were measured as routine at baseline and 12m.

Analysis of knee relief, QOL and adverse reaction

Lysholm knee (LYS) rating scale was used to evaluate the knee function at baseline and 12m. QOL in patients with OS was measured with a 36-item Short Form Health Status Survey questionnaire (SF-36) at baseline and 12m. SF-36 including four physical and fundamental items were calculated which represent the deviation from the reference population. The higher score by SF-36 and LYS means a better QOL and knee function. A treating physician reviewed the clinical results and any discomfort at each visit.

Statistical Analysis Plan

The predetermined primary end point was the difference in the change in BMD of the lumbar spine between the two groups. Sixty four sample size was assumed to achieve 80% power to detect non-inferiority using a one-sided two sample t-test. The margin of non-inferiority is 0.5% percent. The true difference between the means is assumed to be 0. The significance level (alpha) of the one sided test is 0.025. The data were drawn from population with standard deviations of 0. Consider the 10% loss of

follow-up rate, group sample size was 70 cases.

Continuous data are expressed as the mean ±standard deviation. Independent sample t-test by SPSS 22 was used to compare the basic information, clinical characteristics within groups at baseline and the difference values of BMD between that at baseline and 6m and 12m after treatment. Differences in BMD, QOL by SF-36 questionnaire, bone turnover marks and other laboratory results were determined using a paired t-test (one-sided tests) and Mann-Whitney U test. A Fisher exact test was used to compare the adverse events. Pearsman Rho was used to analyze the correlation of lumbar uptake of $Na^{18}F$ and BMD/T value by DXA. P value <0.05 was considered statistically significant.